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14. ABSTRACT The COMBAT study is a randomized clinical trial evaluating the early administration of plasma compared to the standard of care. Over the past one year, we have obtained FDA approval, are in process of obtaining the Colorado Multiple Institutional Review Board approval, and have submitted our protocol to HRPO for approval. We have tested the equipment to be placed on the ambulance and refined the electrical and mechanical components. Furthermore, we have developed an ambulance prototype to test the equipment and operating procedures to ensure efficient and complete data and sample collection.					
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1. INTRODUCTION: *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Bleeding is the most preventable cause of death in trauma patients. Coagulopathy has been documented in up to one third of trauma patients upon arrival to the emergency department. The mechanism of trauma induced coagulopathy (TIC) has yet to be elucidated. Presumptive early administration of plasma has been suggested to improved outcomes in observational studies, but no randomized clinical trial has been conducted to date comparing the administration of early plasma to the current standard of care. In this research study, trauma patients who meet eligibility criteria, defined as field systolic blood pressure (SBP) ≤ 70 mmHg or 71-90mmHg with HR ≥ 108 bpm, will be randomized to receive plasma or intravenous crystalloid, the current standard of care, as the initial resuscitation fluid. Our hypothesis is that the administration of plasma early will attenuate TIC, leading to improved outcomes.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

Coagulopathy; trauma-induced coagulopathy; plasma; resuscitation

3. OVERALL PROJECT SUMMARY: *Summarize the progress during appropriate reporting period (single annual or comprehensive final). This section of the report shall be in direct alignment with respect to each task outlined in the approved SOW in a summary of Current Objectives, and a summary of Results, Progress and Accomplishments with Discussion. Key methodology used during the reporting period, including a description of any changes to originally proposed methods, shall be summarized. Data supporting research conclusions, in the form of figures and/or tables, shall be embedded in the text, appended, or referenced to appended manuscripts. Actual or anticipated problems or delays and actions or plans to resolve them shall be included. Additionally, any changes in approach and reasons for these changes shall be reported. **Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) requires review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.***

- We obtained approvals from 3 different entities: FDA, COMIRB, including community consultation, and HRPO. We received FDA approval on Sept 20, 2012. IRB approval for the community consultation plan implementation was received on 12/13/12. The community consultation and public disclosure plan was conducted from 1/2/13 to 5/1/13. We did a total of 11 community meetings, handed out flyers to the homeless, done a radio interview, newspaper interview, and updated the website. Two interim analyses were submitted to the IRB to track our progress. Final COMIRB approval is pending minor modification.
- We developed a data collection form accompanied by a data dictionary.
- We hired and started training the PRAs/lab techs. In addition to laboratory procedures, they are learning to fill out the data collection form, and beta testing the data dictionary. We initiated the PRA training necessary to accomplish the goals outlined in Year 1 (pre-data acquisition phase, projected for Quarter 2 and 3, (November 2012 – February 2013).

- We have refined the technical specifications of the equipment to be applied in the ambulance and made a prototype to field test the electrical, mechanical and ergonomics of the installed equipment.

4. KEY RESEARCH ACCOMPLISHMENTS: *Bulleted list of key research accomplishments emanating from this research. Project milestones, such as simply completing proposed experiments, are not acceptable as key research accomplishments. Key research accomplishments are those that have contributed to the major goals and objectives and that have potential impact on the research field.*

- Initial IRB application – submitted 08-10-2012
- Obtained the IND, FDA approval, 09-20-2012
- Amendment to IND application 15216 in response to Non-Clinical Hold Comments – submitted 10-22-2012
- 1st Full Board Initial IRB review – meeting 10-26-2012
- 1st IRB protocol deferral – received 11-12-2012
- 2nd IRB study response – submitted 11-19-2012
- 2nd Full Board Initial IRB review – meeting 11-30-2012
- IRB protocol deferral with approval for community consultation plan implementation - received 12-13-2012
- HRPO submission of IND, IRB, CITI training and CV of PI and Co-Investigators – sent 01-02-2013
- Conduction of Community Consultation and Public Disclosure (CCPD)– from 1-2-13 -5/1/13
- Contacted several organizations requesting to present the study
- Community outreach meetings-11 in total including Safety Education and Services Committee of the Denver City Council
- Submission of First Interim CCPD Report-submitted 2-12-14
- Submission of Second Interim CCPD Report-submitted 2-28-13
- Submission of Final Interim CCPD Report-submitted 3-31-13
- Spanish translation of Community Consultation documents
- Completed Community Consultation and Public Disclosure (CCPD)– on 5-1-13
- Submission of Response to Deferral Comments to COMIRB 5-1-13
- Received study approval pending submission of minor modifications 5-23-13
- Continued communication and submission of necessary documents to reviewers at HRPO
- RED Cap data collection forms created, refined, and currently being beta tested and improved
- Completed bench testing of equipment, including electrical requirements.
- Ambulance prototype made and currently being tested

5. CONCLUSION: *Summarize the importance and/or implications with respect to medical and /or military significance of the completed research including distinctive contributions, innovations, or changes in practice or behavior that has come about as a result of the project. A brief description of future plans to accomplish the goals and objectives shall also be included.*

We have made great progress to refine the procedures, equipment, and logistics of implementing the research study. With the ambulance prototype, we can better test the procedures and logistics to further refine the operating protocol to ensure the best collection of data and protection of subjects.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

- a. *List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry shall include the author(s), article title, journal name, book title, editors(s), publisher, volume number, page number(s), date, DOI, PMID, and/or ISBN.*

(1) *Lay Press:*

(2) *Peer-Reviewed Scientific Journals:*

(3) *Invited Articles:*

(4) *Abstracts:*

Moore, EE, Chin, TL, Chapman, MC, Gonzalez, E, Moore, HB, Silliman, CC, Sauaia, A, Banerjee, A. **Plasma First in the Field for Postinjury Hemorrhagic Shock. Shock (manuscript submitted).**

Lee, L, Moore, EE, Hansen, K, Silliman, CS, Chandler, JG, Banerjee, A. **It's Not Your Grandfather's Field Plasma. Surgery 2013; 153: 857-60.**

- b. *List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

3rd Annual Remote Damage Control Resuscitation (RDCR) Symposium, June 17 – 19, 2013, Bergen, Norway*

7. INVENTIONS, PATENTS AND LICENSES: *List all inventions made and patents and licenses applied for and/or issued. Each entry shall include the inventor(s), invention title, patent application number, filing date, patent number if issued, patent issued date, national, or international.*

Nothing to report

8. REPORTABLE OUTCOMES: *Provide a list of reportable outcomes that have resulted from this research. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. This list may include development of prototypes, computer programs and/or software (such as databases and animal models, etc.) or similar products that may be commercialized.*

1. Development of a prototype ambulance that is equipped to thaw plasma in the field
2. Development of a data collection tool within REDCap for the COMBAT study

9. OTHER ACHIEVEMENTS: *This list may include degrees obtained that are supported by this award, development of cell lines, tissue or serum repositories, funding applied for based on work supported by this award, and employment or research opportunities applied for and/or received based on experience/training supported by this award. For each section, 4 through 9, if there is no reportable outcome, state "Nothing to report."*

NIH/NHLBI, 1 UM1 HL120877-01, Analysis and Characterization of Trauma-Induced Coagulopathy, PI: Kenneth G. Mann, MD

10. REFERENCES: *List all references pertinent to the report using a standard journal format (i.e., format used in Science, Military Medicine, etc.).*

Not applicable

11. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

See attached

NOTE:

TRAINING OR FELLOWSHIP AWARDS: *For training or fellowship awards, in addition to the elements outlined above, include a brief description of opportunities for training and professional development. Training activities may include, for example, courses or one-on-one work with a mentor. Professional development activities may include workshops, conferences, seminars, and study groups.*

Not Applicable

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.*

Not Applicable

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.*

Not Applicable

MARKING OF PROPRIETARY INFORMATION: *Data that was developed partially or exclusively at private expense shall be marked as "Proprietary Data" and Distribution Statement B included on the cover page of the report. Federal government approval is required before including Distribution Statement B. The recipient/PI shall coordinate with the GOR to obtain approval. REPORTS NOT PROPERLY MARKED FOR LIMITATION WILL BE DISTRIBUTED AS APPROVED FOR PUBLIC RELEASE. It is the responsibility of the Principal Investigator to advise the GOR when restricted limitation assigned to a document can be downgraded to "Approved for Public Release." DO NOT USE THE WORD "CONFIDENTIAL" WHEN MARKING DOCUMENTS. See term entitled "Intangible Property – Data and Software Requirements" and https://mrmc.amedd.army.mil/index.cfm?pageid=researcher_resources.technical_reporting for additional information.*

Not Applicable

Evidence-Based Surgical Hypothesis

It's not your grandfather's field plasma

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Initiating prehospital resuscitation with plasma in patients with trauma-associated hemorrhagic shock will result in more rapid and durable clot formation and, thus, the need for fewer packed cell infusions, less frequent use of cryoprecipitate, and more ventilator-free hospital days compared with those of patients randomized to standard crystalloid field resuscitation. (Surgery 2013;153:857-60.)

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BLOOD'S PREEMINENCE

HEMORRHAGE IS THE MOST PREVENTABLE CAUSE of trauma-related fatalities.¹ The uniqueness of blood's oxygen-carrying red cells in combination with pro-coagulant factors and oncotic properties became more apparent in the interim between World Wars I and II. In World War II, resuscitation with reconstituted, freeze-dried plasma (FDP) during evacuation was an effective in-transit strategy, but required blood availability at a field hospital to achieve its full potential. Physicians serving in Korea and Vietnam had ready access to blood, but triple isotope studies of Shires et al² in 1961 defined a third-space fluid loss that prompted an American Vietnam military hospital policy of infusing a ratio of 3 L of crystalloid for each unit of blood transfused.

Casualties reaching combat hospitals have had a progressively better chance of survival in successive wars, which rebounded in Vietnam (Fig 1).³ The comfortable explanation was that unsalvageable patients who would have died in the field in previous wars were now reaching a care center. A plausible alternative is that potentially salvageable patients were more likely to bleed from dilutive coagulopathy, despite frequent use of fresh-drawn whole blood.

Multiple studies now support restricted crystalloid resuscitation, and Ley et al⁴ identified ≥ 1.5 L as being associated with increased mortality among 3000 trauma patients. Brohi et al's⁵ often quoted 24.4% incidence of trauma-associated, acute coagulopathy on admission to the emergency department at a median of 73 minutes (interquartile range, 57–75) after injury involved patients who had all received <1,500 mL of prehospital crystalloid. This report reignited interest in proscribed transfusion ratios, but with a shift in emphasis from crystalloid to FFP for preemptively addressing trauma-associated, acute coagulopathy. Giving FFP soon after injury is paramount, because the survival benefit is primarily in the first 24 hours.¹ Yet, ratios of FFP to packed RBC are based typically on 24-hour treatment intervals and, therefore, are not truly preemptive. They also are often not achieved because of clinical exigencies and fall behind as less effective “catch-up therapy.” For example, the statistical model of Holcomb et al,⁶ derived from their multicenter, retrospective study indicates specifying a 1:1 ratio would be needed to ensure an actual delivery ratio of 1:2.

PLASMA, NATURE'S “ORGANIC” PROCOAGULANT COLLOID THEN AND NOW

Plasma, unlike blood, can be preserved by freezing at -18°C (fresh frozen plasma [FFP]) or FDP by spraying in vacuum (lyophilization or cryodesiccation). Because freeze or spray drying removes CO_2 and water, FDP should be reconstituted with a weak acid. FDP has a room temperature shelf-life measured in years and can be used for 24 hours after reconstitution, which takes <5 minutes. World War II FDP was derived from

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WIAs Dying of Wounds	
Conflict	Percent
Crimean War, 1854-56	20.0
US Civil War (North), 1861-65	14.1
Franco-Prussian War, 1870-71	13.6
Spanish American War, 1898	6.7
World War I, 1914-18	6.1
World War II, 1939-45*	4.5
Korean War, 1950-53*	2.5
Vietnam Conflict, 1965-75*	3.6

*US troops only

Fig 1. Troops wounded in action (WIA) who do not survive after reaching a medical treatment facility are categorized as dying of wounds (DOW), as opposed to having been killed in action (KIA).³ (Color version of figure is available online.)

pooled plasma, which increased the probability of transmission of viral hepatitis at a time when contemporary donor screening was not sufficient to make even single-donor plasma 100% safe, particularly when donors were paid. The emergence of the acquired immunodeficiency syndrome in the 1980s and subsequent identification of the human immunodeficiency virus ensured the apparent permanent retirement of FDP. Nucleic acid testing has brought it back by ensuring that fresh drawn pooled plasma is virtually virus free before its preservation.

FFP designates plasma that has been frozen within 6–8 hours of collection and is typically single donor plasma. FFP has been largely supplanted by FP24, which can be frozen within 24 hours of collection, allowing for large mobile blood drives. Both FFP and FP24 must be stored at -18°C , have a storage limit of 12 months (7 years at -65°C), can take 15 minutes to thaw, and once thawed, should be used within 24 hours. Freeze or spray dried (lyophilized) plasma (FDP) has been continuously available in South Africa and France since 1998 as a solvent-detergent-treated, FDP (S/DFDP). This preparation has gone through multiple processing iterations, mainly in Europe, and is now available from ≥ 3 European manufacturers.⁷ FFP, FP24, and S/DFDP all contain substantially less fibrinogen than fresh plasma (Fig 2).⁸ FP24 differs from FFP by having insufficient factor VIII and is contraindicated for treating hemophiliac bleeding. S/DFDP is relatively deficient in von Willebrand factor, protein S, α_1 -antitrypsin, and α_2 -antiplasmin. Diminished protein S was blamed for occasional thromboembolic events, and

paradoxically increased bleeding was ascribed to antitrypsin and antiplasmin deficiencies when multiple units of American S/DFDP had been given to patients with severe liver disease, causing its sole manufacturer to cease production in 2002. Neither aberrant event has been observed in patients undergoing liver transplants who have received current European S/DFDP iterations, which have a slightly greater level of plasmin inhibitor.⁷

In the United States, male-only plasma donors have decreased the risk of plasma-induced, transfusion-related acute lung injury (TRALI), but TRALI is still the leading cause of transfusion-related deaths in the United States. In Europe, solvent-detergent treatment of relatively large pools of FDP has eliminated completely the risk of TRALI from plasma (0 incidences after 10^6 infusions) by diluting and neutralizing leukocyte antibodies and washing out activated lipids.⁷ The treatment removes >5 logs of abnormal prion protein and most enveloped viruses, including HIV, hepatitis C, and West Nile. Pooling types A, B, and AB plasma in ratios approximating their relative presence in the population and excluding type O donors also allows A and B antigens to neutralize naturally occurring anti-A and anti-B hemagglutinins as well as possible anti-idiotypic antibodies, thereby constituting a universal, pathogen-reduced plasma for all blood types that also minimizes allergic reactions.⁹

The German and French armies are using S/DFDP in Afghanistan and have used it effectively in treating several US Special Forces casualties. The US Department of Defense would like to have it, but the US Food and Drug Administration is skeptical and maintains a high bar for approval of any new FDP format. Consequently, European manufacturers and the former American manufacturer are reluctant to undertake the expensive studies that might allow them to enter or reenter the US market.

PLASMA PROTEOMICS

The protein concentration of plasma is approximately 65 g/L. Albumin, transferrin, and immunoglobulins comprise the majority (up to 80%) of protein. The next most abundant 50 proteins include (1) additional transport and apolipoproteins for storage, delivery, and clearance of lipids, iron, and hydrophobic hormone carriers; (2) several protease inhibitors, including members of the serpin family, which inhibit classic serum proteases, coagulation, and fibrinolytic factors, and many matrix metalloproteases; (3) coagulation factors; (4) acute phase components; and (5)

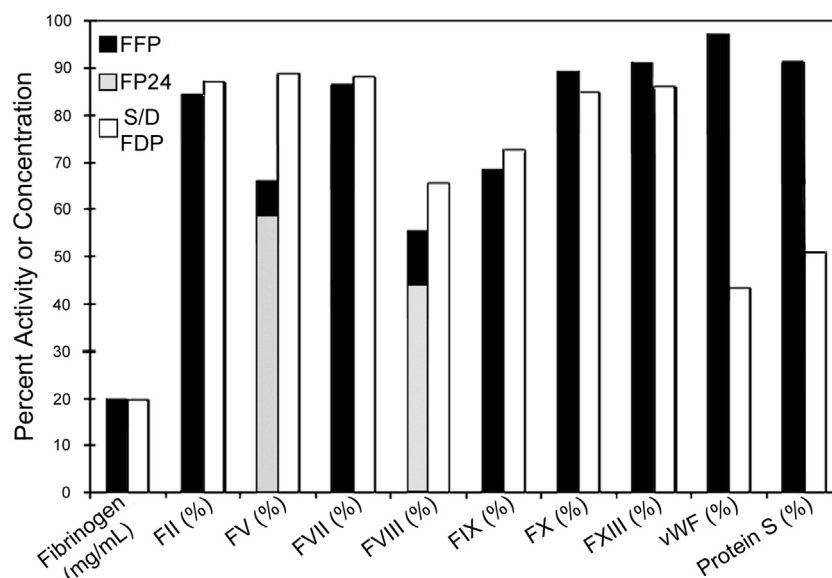


Fig 2. Percent retained coagulation factor activity in thawed FFP (freshly drawn plasma frozen within 8 hours); in FP24 for factors V and VIII, where freezing within 24 hours differs from FFP; and in room temperature-stored, reconstituted solvent-detergent treated freeze dried plasma (S/DFDP). *vWF*, von Willebrand factor.⁸

enzymes responsible for the bioconversion of small molecules.

A proteomic analysis of female versus male plasma revealed female plasma to have approximately twice the concentrations of anti-proteases, α_2 -macroglobulin, and α_1 -antitrypsin, which oppose enzymatic clot degradation and males to have almost 15-fold more transgelin-2.¹⁰ The latter “gels” actin at a ratio of 1:6 preventing the formation of actin filaments that, if formed in the circulation, get trapped in the pulmonary capillaries.

We and others have observed significant differences in these more abundant plasma components, in various animal models of trauma research as well as in clinical samples. Qian et al¹¹ identified 110 of 313 proteins that exhibited a significant change in abundance in the plasma of 15 severe burn patients compared with a pool of healthy controls. The most striking findings were that the abundant protease inhibitors α_1 -antichymotrypsin, α_1 -antitrypsin-related protein, plasma protease C1 inhibitor, and β_2 -microglobulin all increased with injury, whereas antithrombin III, α_2 antiplasmin, and inter- α -trypsin inhibitor heavy chains-H1 and -H2 were decreased uniformly.¹¹ The protective mode of action of plasma does not necessarily reflect the beneficial effect of a specific component, but rather the balance of components and their ability to “buffer” a wide range of shock-generated abnormalities. Such abnormalities after shock states include endothelial permeability, inappropriate coagulation, and other protease-protease inhibitor imbalances. Advances in proteomic

techniques make it possible to monitor hundreds to thousands of proteins in a targeted way so that we can begin to understand the role of a fluid as dynamic and complex as plasma in the setting of trauma-associated hemorrhagic shock.¹²

PROPOSAL

It is time to leverage our greater understanding of critical care and the superior safety profile of European universal donor S/DFDP to test the effectiveness of its preemptive field use with a randomized, prospective controlled trial versus standard prehospital crystalloid resuscitation. This study can be done at any busy, level 1 trauma center where severely injured patients are encountered commonly; such patients predictably require whole blood transfusion based on their on-site blood pressure and pulse rates and heuristic observation of such factors as penetrating torso wounds and an unstable pelvis.¹

Ambulances could carry S/DFDP and ascorbic acid solution units for its reconstitution that takes <5 minutes. Trained EMTs could determine eligibility and do the randomization on site. Further management would be in accord with ATLS and local protocols, monitoring coagulation with sequential thromboelastography and coagulation panels. The primary endpoints would be usage of whole blood and components, with ventilator-free days and hospital mortality as secondary endpoints. US Food and Drug Administration regulations for patients with life-threatening medical

conditions where prospective informed consent is not possible can be found in 21 CFR §50.24, which includes descriptions of requisite community consultation and public disclosure that must occur before beginning patient enrollment.

Obtaining US Food and Drug Administration approval for this specific use will require cooperation from a European manufacturer and will not be an easy task. Developing evidence of the superiority of S/DFDP over crystalloid for field resuscitation will not add substantially to the excellent safety profile of the European universal donor S/DFDP. But it could be the lynch pin to engage manufacturer interest and segue into a unique US Department of Defense–European-manufacturer-partnered IND (Investigational New Drug) application, pitting S/DFDP against FP24 US standard of care for generalized use.

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